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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/673,707	01/11/2001	Ira H. Pastan	15280-3561US	3958

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EXAMINER	
ZEMAN, ROBERT A	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/673,707	PASTAN ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *19-24,59-65,79-88,90-97,99 and 101-103* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,11,52-55,57,68-75 and 77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2-3-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-7,9,11,19-24,52-55,57,59-65,68-75,77,79-88,90-97,99 and 101-103.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 1-20-2006 has been entered.

The amendment filed on 9-19-2005 has been entered. Claims 1, 19-24, 52, 55, 59, 68, 74, 79 and 90 have been amended. Claims 8, 10, 56, 58, 66-67, 76, 78, 89, 98 and 100 have been canceled. Claims1-7, 9, 11, 19-24, 52-55, 57, 59-65, 68-75, 77, 79-88, 90-97, 99 and 101-103 are pending. Claims 19-24, 59-65, 79-88, 90-97, 99 and 101-103 remain withdrawn from consideration as being drawn to non-elected inventions. Claims 1-7, 9, 11, 52-55, 57, 68-75 and 77 are currently under examination.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. [1] as follows:

The later-filed application must be an application for a patent for an invention that is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed

application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. PCT/US99/12909 and U.S Application 60/088,860, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The sequence set forth in SEQ ID NO:1 of the instant application differs from those disclosed in the prior-filed applications.

Information Disclosure Statement

The Information Disclosure Statement filed on 2-3-2006 has been considered. An initialed copy is attached hereto.

Objections Withdrawn

The objection to the specification for referring to U.S. patent Applications that have since been issued is withdrawn in light of the amendment thereto.

The objection to the specification for disclosing that SEQ ID NO:1 is the sequence of both the intact 3b3 antibody and a 3b3(Fv) is withdrawn in light of the amendment thereto.

Claim Rejections Withdrawn

The rejection of claims 8, 10, 56, 58, 76 and 78 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in light of the cancellation of claims 8, 10, 56, 58, 76 and 78 and the amendment to claims 55 and 74.

Claim Rejections Maintained

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 1-6, 9, 11, 52-55, 57, 68-72, 74-75 and 77 under 35 U.S.C. 103(a) as obvious over Matsushita et al. (Aids Research and Human Retroviruses Vol. 6 No. 2, 1990, pages 193-203) in view of Barbas et al. (PNAS Vol. 91, 1994, pages 3809-3813 – IDS-5) and Pastan et al. (U.S. Patent 5,458,878 – IDS-5) is maintained for reasons set forth in the previous

Office action in the rejection of claims 1-6, 8-9, 11, 52-55, 57, 68-72 and 74-77. The cancellation of claims 8 and 76 has rendered the rejection of those claims moot.

Applicant argues:

1. Developments in the art after the date of Matsushita's publication would destroy the *prima facie* case of obviousness outlined in the rejection.

2. The examiner does not provide reasons why the CD4-PE40 immunotoxin of the Ramachandran reference and the sCD4-PE40 immunotoxin of the Davey reference are not analogous to the anti-gp120 immunotoxins of the present invention.

3. The Goldstein reference was cited for its retrospective statement as to what persons of skill thought following the publication of the Ramachandran and Davey studies.

4. CD4-P40 would bind only to cells that express the gp120 protein which binds CD4, hence there is no difference between the cells targeted by a CD4 targeted immunotoxin and an anti-gp120 antibody targeted immunotoxin.

5. The unexpected liver toxicity associated with CD4-targeted immunotoxins was not due to the immunotoxin binding to normal CD4 expressing cells as liver cells (hepatocytes) do not normally express CD4. Moreover, since said toxicity was not seen in the animal studies it could not be caused by the targeting of healthy cells along with HIV-infected cells.

6. The post-filing reference by Berger et al. discloses that "the significant but reversible hepatoxicity greatly diminished enthusiasm for CD4-PE40 in particular and for Env-targeted toxins in general".

7. Despite a long felt need for AIDS treatments, only a handful of references pertaining to anti-gp120 immunotoxins or anti-HIV immunotoxins were published between the publication date of

the Matsushita reference and the filing date of the instant application. This is evidence that persons of skill in the art were not motivated to develop anti-gp120 immunotoxins. Applicant's arguments have been fully considered and deemed non-persuasive.

The instant invention is drawn to immunotoxins comprising a cytotoxin (e.g. PE38) attached to an anti-gp120 antibody (e.g. 3B3) having the binding specificity of 3B3. Said antibody can be a dsFv. The instant invention is also drawn to kits and compositions comprising said immunotoxins.

With regard to Points 1-2, the Ramachandran et al. reference is drawn to CD4-PE40 immunotoxins that are not analogous to the instant invention since they target different cellular components. The immunotoxins of the instant invention (and those of the combined art) target cells expressing gp120 on their surface (i.e. infected cells) whereas the CD4-PE40 immunotoxin of Ramachandran et al. target any cell expressing CD4. Hence any "results" based on the application of CD4-PE40 immunotoxin would not have any bearing on the perceived efficacy of immunotoxin based on the combination of the cited references. The same is true for the sCD40-PE immunotoxin disclosed by Davey et al.

With regard to Point 3, the Goldstein et al. reference discloses that Env-target toxins have therapeutic efficacy thus supporting the validity of the Matsushita reference.

With regard to Point 4, contrary to Applicants assertion, CD4-P40 immunotoxins would bind not only to cells expressing gp120, but also to any cell expressing CD4 on its surface.

With regard to Point 5, since the CD4-PE40 immunotoxin would bind to any cell expressing CD4 on its surface, the hepatoxicity would logically be the result of said

immunotoxin binding to healthy cells thereby disrupting some cellular or endocrine cascade present in man but not in the mouse.

With regard to Point 6, Applicants assertion that the failure of CD4-PE immunotoxins to live up to expectations and hence would remove the motivation provided by Matsushita, said assertions are deemed unpersuasive. "Diminished enthusiasm" for a failed treatment modality is common response especially when the expectations of said modality was high. Moreover, the failure of a non-analogous immunotoxin, while it may have been discouraging would not necessarily remove the motivation provided by Matsushita, especially when his immunotoxin (which is analogous to the instant invention) was disclosed to have efficacy. Moreover, Berger et al. disclose that Env-targeted toxins "may also be useful components in drug cocktails". Said statement demonstrates, contrary to Applicant's assertion, there was still interest, and hence motivation, in Env-targeted immunotoxins.

With regard to Point 7, the "long felt need" for AIDS treatments was met by the teachings of Matsushita and would provide additional motivation for the skilled artisan to further refine the teachings of Matsushita.

As outlined previously, Matsushita et al. disclose anti-pg120 immunotoxins comprising the 0.5β antibody coupled to the *Pseudomonas* exotoxin (see abstract). Matsushita et al. differs from the instant invention in that they don't disclose the use of the 3B3 antibody or the use of altered PE40. Barbas et al. disclose a human antibody to gp120 (3B3) with broad strain cross-reactivity (see page 3812-3813). Pastan et al. disclose modifications of the carboxyl terminus of the PE molecule resulting in increased cytotoxicity (see abstract and column 3, line 27 to column 4, line 10). Given that Matsushita et al. suggest the use of an antibody that is broadly reactive

with a number of HIV isolates (see page 200), it would have been obvious for one of ordinary skill in the art to use the 3B3 antibody in the immunotoxin disclosed by Matsushita et al. Moreover, it would a have been equally obvious for one of ordinary skill to incorporate the PE modifications disclosed by Pastan et al. in order to take advantage of the resulting increase in cytotoxicity. It should be noted that while the incorporation of immunotoxins in kits is not explicitly disclosed by Matsushita et al., said incorporation would have been obvious to one of ordinary skill in the art in order to reduce cost and ease preparation time. It should be noted that while the sequence of the 3B3 antibody is not explicitly disclosed, it is deemed in absence of evidence to the contrary to be the same as that of the 3B3 of the instant application (SEQ ID NO:1).

New Grounds of Rejection

35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9, 11, 52-55, 57, 68-75 and 77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "SEQ ID NO:1" within parentheses in claims 1, 52, 55, 68 and 74 render said claims indefinite. It is unclear what said recitation encompasses (i.e. whether said recitation is to be interpreted as open or closed claim language.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ROBERT ZEMAN
PATENT EXAMINER

April 4, 2006